STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 97805

TO: Jennifer Kim **Location: 2d17 / 2b19** **Tuesday, July 01, 2003** **Art Unit: 1617** **Phone: 308-2232** **Serial Number: 10 / 031797**	**From: Jan Delaval** **Location: Biotech-Chem Library** **CM1-1E07** **Phone: 308-4498** **jan.delaval@uspto.gov**

Search Notes

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

Jan Delaval

Access DB# 97805

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jennifer Kim Examiner #: 77469 Date: 7/1/03
Art Unit: 1617 Phone Number 30 8-2232 Serial Number: 10/031,997
Mail Box and Bldg/Room Location: 2D17 Results Format Preferred (circle): PAPER DISK E-MAIL
2B19

If more than one search is submitted, please prioritize searches in order of need. ME'

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Use of antiprogestagens in combined therapy

Inventors (please provide full names): Bennink et al.

Earliest Priority Filing Date: 4/29/99

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

1) Please search claims 5+6.

2) Please search claims 10-18

3) Please provide a therapeutic use of active agent (Org 33245).

THX,

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

****

STAFF USE ONLY

Searcher: an
Searcher Phone #: 4495
Searcher Location:
Date Searcher Picked Up: 7/1/03
Date Completed: 7/1/03
Searcher Prep & Review Time:
Clerical Prep Time: 10
Online Time: + 20

Type of Search

NA Sequence (#)
AA Sequence (#)
Structure (#) ✓
Bibliographic
Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable

STN ✓
Dialog
Questel/Orbit
Dr.Link
Lexis/Nexis
Sequence Systems
WWW/Internet
Other (specify)

PTO-1590 (8-01)

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FILE 'REGISTRY' ENTERED AT 14:03:08 ON 01 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   30 JUN 2003  HIGHEST RN 540462-79-1
DICTIONARY FILE UPDATES:  30 JUN 2003  HIGHEST RN 540462-79-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

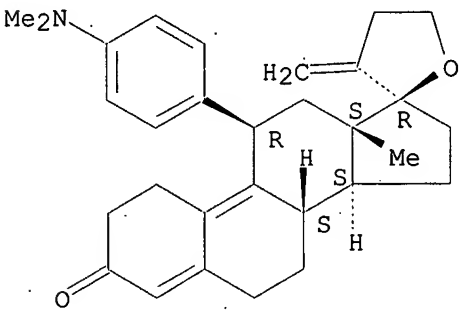
Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   155768-15-3  REGISTRY
CN   19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-
     epoxy-, (11.beta.,17.alpha.)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Spiro[17H-cyclopenta[a]phenanthrene-17,2'(3'H)-furan],
     19,24-dinorchola-4,9,20-trien-3-one deriv.
OTHER NAMES:
CN   Org 33245
FS   STEREOSEARCH
MF   C30 H37 N O2
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL

Absolute stereochemistry.
```



Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              4 REFERENCES IN FILE CA (1957 TO DATE)
              4 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE   1:  136:274272
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REFERENCE 2: 133:345161

REFERENCE 3: 121:231157

REFERENCE 4: 121:35986

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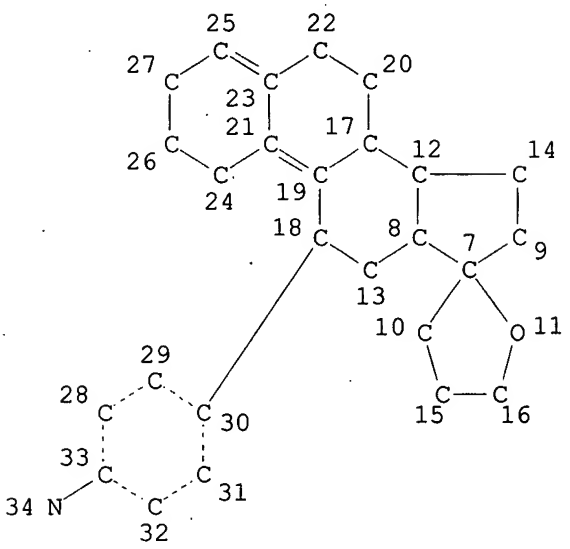
L7 STR



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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 28

STEREO ATTRIBUTES: NONE
L8 36 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED 62 ITERATIONS 36 ANSWERS
SEARCH TIME: 00.00.01

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SET COST OFF

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L2 0 S 155768-15-3/CRN
L3 STR
L4 2 S L3
L5 31 S L3 FUL
SAV L5 JKIM031/A
L6 27 S L5 AND 1/NC
L7 STR L3
L8 36 S L7 FUL
SAV L8 JKIM031A/A

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L9            32 S L8 AND 1/NC
L10            5 S L9 NOT L6
L11            2 S L10 AND 2/N
L12            3 S L10 NOT L11
L13            1 S L6 AND C30H37NO2
L14           26 S L6 NOT L1,L13
L15            3 S L11,L13
L16            4 S L5,L8 NOT L6,L9
L17            2 S L16 AND MXS/CI

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L22           35 S E4-E9
                 E BENNINK/AU
                 E COELINGH/AU
L23           45 S E4-E7
                 E COELING/AU
L24            2 S E4,E5
                 E DECKERS G/AU
L25           28 S E3-E5,E8,E9
                 E DOLS P/AU
L26           13 S E3-E9
                 E ORLEMANS E/AU
L27           13 S E4-E6
                 E SCHOONEN W/AU
L28           50 S E3-E7
                 E AKZO/PA,CS
L29         4677 S E3,E4 OR AKZO?/PA,CS
L30            6 S L21 AND L22-L29
L31            7 S L21,L30
                 E WO2000-EP3747/AP,PRN
L32            1 S E3,E4
                 E EP99-99201390/AP,PRN
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L33            1 S E4
L34            7 S L31-L33

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L35            3 S L21

     FILE 'REGISTRY' ENTERED AT 14:03:08 ON 01 JUL 2003

=> d ide can tot 111

L11  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2003 ACS
RN   158294-09-8 REGISTRY
CN   19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-
     epoxy-, oxime, (3Z,11.beta.,17.alpha.)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Spiro[17H-cyclopenta[a]phenanthrene-17,2'(3'H)-furan],
     19,24-dinorchola-4,9,20-trien-3-one deriv.
FS   STEREOSEARCH
MF   C30 H38 N2 O2
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.
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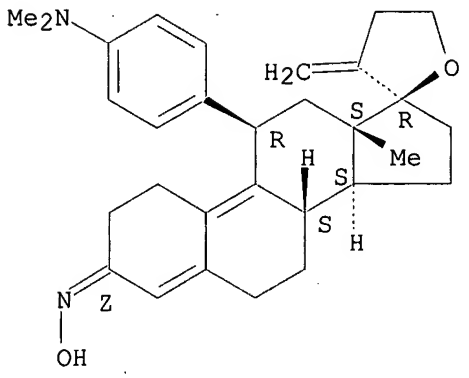


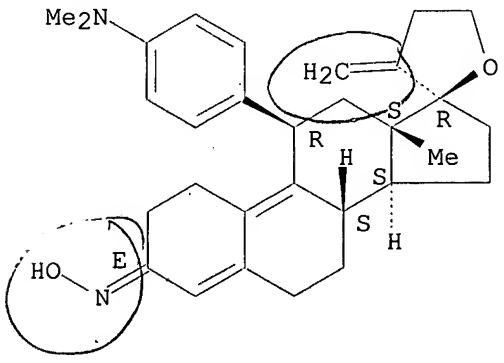
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 121:231157

L11 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 158294-08-7 REGISTRY
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3E,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[17H-cyclopenta[a]phenanthrene-17,2'(3'H)-furan], 19,24-dinorchola-4,9,20-trien-3-one deriv.
FS STEREOSEARCH
MF **C30 H38 N2 O2**
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 121:231157

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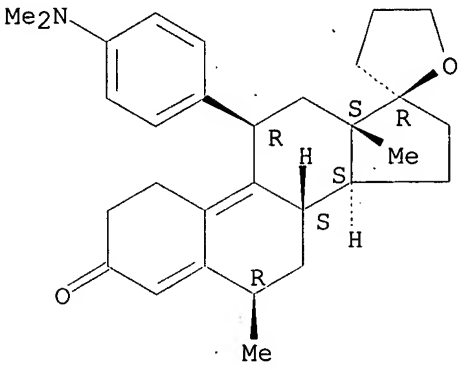
L17 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS

RN 225511-57-9 REGISTRY
CN Spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methyl-, (6.beta.,11.beta.,17.beta.)-, mixt. with (17.alpha.)-17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 19-Norpregna-4,15-dien-20-yn-3-one, 17-hydroxy-11-methylene-, (17.alpha.)-, mixt. contg. (9CI)
FS STEREOSEARCH
MF C30 H39 N O2 . C21 H24 O2
CI **MXS**
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 118968-41-5
CMF C30 H39 N O2

Absolute stereochemistry.



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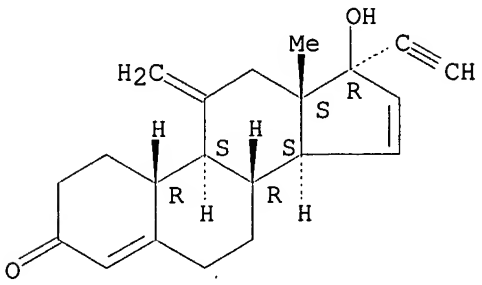
CRN 110072-15-6
CMF C21 H24 O2

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 131:9627

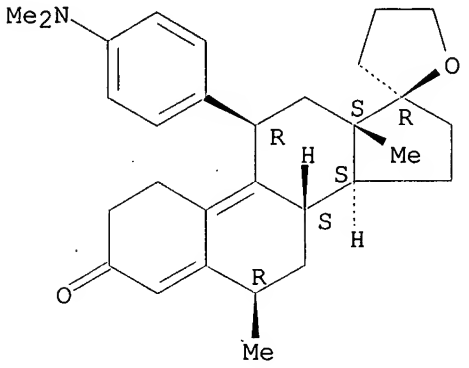
L17 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 225511-56-8 REGISTRY

CN Spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methyl-, (6.beta.,11.beta.,17.beta.)-, mixt. with (17.alpha.)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 18,19-Dinorpregn-4-en-20-yn-17-ol, 13-ethyl-11-methylene-, (17.alpha.)-, mixt. contg. (9CI)
FS STEREOSEARCH
MF C30 H39 N O2 . C22 H30 O
CI **MXS**
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 118968-41-5
CMF C30 H39 N O2

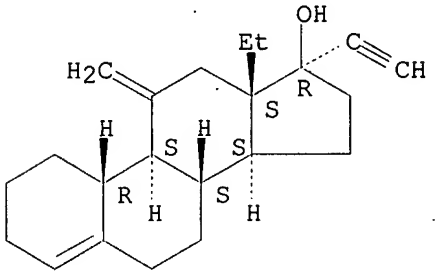
Absolute stereochemistry.



CM 2

CRN 54024-22-5
CMF C22 H30 O

Absolute stereochemistry. Rotation (+).



1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 131:9627

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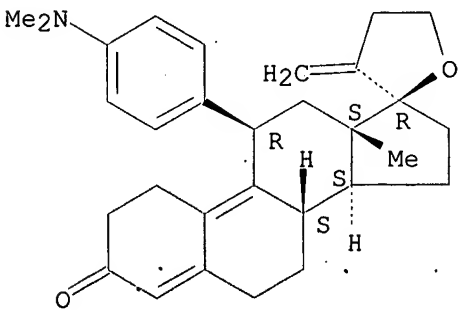
FILE 'USPAT2' ENTERED AT 14:03:54 ON 01 JUL 2003

=> d bib abs hitstr tot l35

L35 ANSWER 1 OF 3 USPATFULL
AN 1998:162499 USPATFULL
TI 17-spiromethylene steroids
IN Hamersma, Johannes Antonius Maria, Oss, Netherlands
Orlemans, Everardus Otto Maria, Oss, Netherlands
Rewinkel, Johannes Bernardus Maria, Oss, Netherlands
PA Akzo Nobel N.V., Arnhem, Netherlands (non-U.S. corporation)
PI US 5854235 19981229
AI US 1997-962798 19971103 (8)
RLI Division of Ser. No. US 1993-98665, filed on 28 Jul 1993, now patented, Pat. No. US 5712264
PRAI EP 1992-202339 19920729
EP 1993-201657 19930610
DT Utility
FS Granted
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Kifle, Bruck
LREP Gormley, Mary E.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1356
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a steroid derivative which steroidal skeleton is bound at carbon atom 17 to a spiromethylene ring of the formula: ##STR1## wherein R.sub.a and R.sub.b are independently selected from the group consisting of hydrogen, methyl, and halogen; m is 1 or 2; and the asterisk denotes carbon atom 2 of the spiromethylene ring which is carbon atom 17 (or carbon atom 17.alpha. of a homosteroid skeleton) of the steroid. The steroids have progestational or antiprogestational activity.

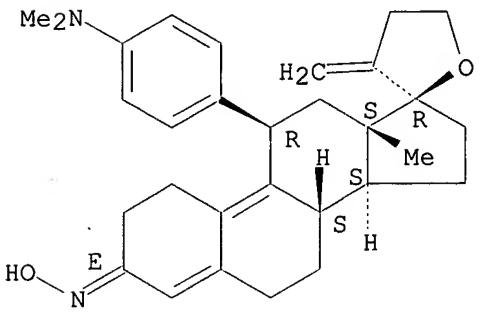
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **155768-15-3P 158294-08-7P 158294-09-8P**
(prepn. of, for its progestational or antiprogestational activity)
RN 155768-15-3 USPATFULL
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



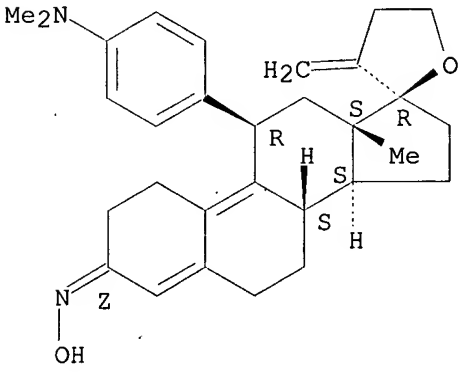
RN 158294-08-7 USPATFULL
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3E,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 158294-09-8 USPATFULL
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3Z,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L35 ANSWER 2 OF 3 USPATFULL
AN 1998:9491 USPATFULL
TI 17-spiromethylene steroids
IN Hamersma, Johannes Antonius Maria, Oss, Netherlands
Orlemans, Everardus Otto Maria, Oss, Netherlands
Rewinkel, Johannes Bernardus Maria, Oss, Netherlands
PA Akzo Nobel N.V., Arnhem, Netherlands (non-U.S. corporation)
PI US 5712264 19980127
AI US 1993-98665 19930728 (8)
PRAI EP 1992-202339 19920729
EP 1993-201657 19930610
DT Utility
FS Granted
EXNAM Primary Examiner: Berch, Mark L.; Assistant Examiner: Kifle, Bruck
LREP Gormley, Mary E.
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1606
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a steroid derivative which steroidal skeleton is bound at carbon atom 17 to a spiromethylene ring of the formula: ##STR1## wherein R.sub.a and R.sub.b are independently selected from the

group consisting of hydrogen, methyl, and halogen; m is 1 or 2; and the asterisk denotes carbon atom 2 of the spiromethylene ring which is carbon atom 17 (or carbon atom 17.alpha. of a homosteroid skeleton) of the steroid. The steroids have progestational or antiprogestational activity.

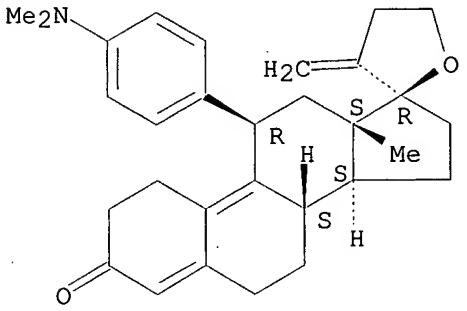
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **155768-15-3P 158294-08-7P 158294-09-8P**
(prepn. of, for its progestational or antiprogestational activity)

RN 155768-15-3 USPATFULL

CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

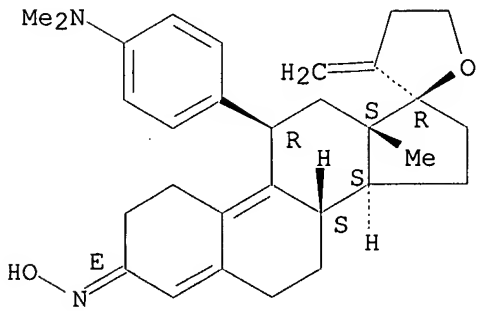
Absolute stereochemistry.



RN 158294-08-7 USPATFULL

CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3E,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

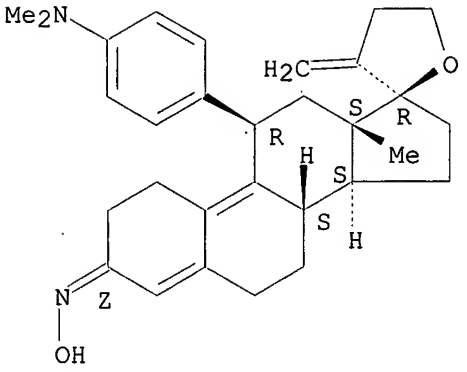
Absolute stereochemistry.
Double bond geometry as shown.



RN 158294-09-8 USPATFULL

CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3Z,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L35 ANSWER 3 OF 3 USPATFULL
AN 94:20310 USPATFULL
TI 17-spirofuran-3'-ylidene steroids
IN Hamersma, Johannes A. M., Oss, Netherlands
Orlemans, Everardus O. M., Oss, Netherlands
PA Akzo N.V., Arnhem, Netherlands (non-U.S. corporation)
PI US 5292878 19940308
AI US 1992-994039 19921221 (7)
PRAI EP 1991-203366 19911220
DT Utility
FS Granted
EXNAM Primary Examiner: Killos, Paul J.
LREP Blackstone, William M.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 381
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to an antiprogestin 17- spirofuran-3'-ylidene steroid having the formula ##STR1## p0 R.sub.1 is NR.sub.2 R.sub.3, lower acyl, OH, SH, O-lower alkyl or S(O).sub.n -lower alkyl wherein n is 0-2;

R.sub.2 and R.sub.3 are independently selected from hydrogen and lower alkyl;

R.sub.4 is hydrogen or lower alkyl;

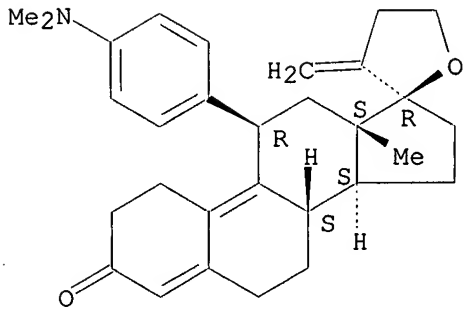
R.sub.5 is O, (H,H), (H,OH), (H,O-lower acyl), or NOH;

R.sub.6 and R.sub.7 are both hydrogen, or one is hydrogen and the other lower alkyl; and

the twitched line represents an .alpha. or .beta. bond.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **155768-15-3P**
(prepn. of, as antiprogestin)
RN 155768-15-3 USPATFULL
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 1 Jul 2003  VOL 139 ISS 1
FILE LAST UPDATED: 30 Jun 2003  (20030630/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d all hitstr tot l34

L34  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2003 ACS
AN   2002:240960  HCAPLUS
DN   136:274272
TI   Ligand-dependent regulation of transgene expression by a plasmid-based
     autoinducible GeneSwitch system for gene therapy application
IN   Abruzzese, Ronald V.; Mehta, Vidya; Nordstrom, Jeffrey L.
PA   Valentis, Inc., USA
SO   PCT Int. Appl., 101 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C12N015-00
CC   3-2 (Biochemical Genetics)
     Section cross-reference(s): 1, 9
FAN.CNT 1
     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
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PI   WO 2002024899     A2   20020328       WO 2001-US30305  20010925
     WO 2002024899     A3   20021212
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             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001096354 A5 20020402 AU 2001-96354 20010925

PRAI US 2000-235030P P 20000925
US 2001-260781P P 20010110
US 2001-278281P P 20010323
WO 2001-US30305 W 20010925

AB The present invention provides an improved mol.-switch, inducible-expression system for regulating the expression of a nucleic acid sequence in gene therapy under conditions in which tight control of expression is of particular importance. In one aspect of the invention, a system is provided wherein expression of the gene to be induced is characterized by low or undetectable expression or biol. effect in the absence of the inducer, but in the presence of the inducer, is characterized by efficient induction of expression or biol. effect. In another aspect of the present invention, a method is provided that induces a measure of tolerance to transgenic proteins, thus making longterm administration of the protein by gene therapy or recombinant protein possible and effective. In one embodiment of the invention, the mol.-switch, inducible-expression system comprises two nucleic acid or expression cassettes. The first expression cassette includes a promoter driving the expression of a mol. switch protein. The mol. switch protein is a chimeric or fusion protein that includes a mutated DNA binding domain characterized by a modification that eliminates a domain having a potential for autodimerization in the absence of an inducer while retaining those domains required for recognition of its cognate DNA sequence on the promoter of the second expression cassette. In one embodiment the DNA binding domain is a truncated GAL-4 DNA binding domain. The fusion protein further comprises a transactivation domain, and a mutated ligand-binding domain of a steroid-hormone receptor capable of being activated by a non-natural ligand inducer such as mifepristone. In a one embodiment, the promoter is a tissue-specific promoter such as .alpha.-actin promoter specific for muscle tissues. The first expression cassette may also include 5' untranslated regions, synthetic introns, and poly (A) signals that increase the fidelity and level of expression of the mol. switch gene. The second expression cassette includes a transgene encoding a desired gene product controlled by an inducible promoter comprising GAL-4 DNA-binding sites linked to a minimal promoter. The second expression cassette may also include 5' untranslated regions, synthetic introns, and poly (A) signals that increase the fidelity and level of expression of the transgene to be induced. In another embodiment of the invention, the inducible expression system is applied in vivo to effect expression of a transgene for gene therapy purposes. In one embodiment the inducible expression system is formulated with nonionic or anionic polymers and injected into an animal or human. Enhancement of transfection in vivo may be obtained with in vivo electroporation. The authors investigated the ability of an improved mifepristone-dependent GeneSwitch system to regulate the expression of genes for three therapeutic proteins: factor IX, IFN-.alpha., and erythropoietin. The GeneSwitch system consisted of two plasmids, one encoding the chimeric GeneSwitch protein, the other an inducible transgene. When the constitutive CMV promoter of the GeneSwitch plasmid was replaced by an autoinducible promoter consisting of four copies of GAL4 DNA binding sites linked to a minimal thymidine kinase promoter, the tightness of transgene regulation was improved by an order of magnitude. Quant. RT-PCR anal. of GeneSwitch mRNA confirmed that the autoinducible promoter was responsive to mifepristone. The authors demonstrated the ability of the improved GeneSwitch system to regulate the expression of VEGF or erythropoietin in

a biol. relevant manner after delivery of plasmids to the hindlimb muscle of adult mice. This ability of the autoinducible GeneSwitch system to regulate the expression of therapeutic proteins in mice indicates its potential for use in human gene therapy applications.

ST ligand transgene expression plasmid autoinducible GeneSwitch system gene therapy; mifepristone regulation erythropoietin expression muscle actin promoter

IT Genetic element
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(5'-untranslated region; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GAL4, truncated DNA binding domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NF-.kappa.B (nuclear factor of .kappa. light chain gene enhancer in B-cells), p65, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ORF-10, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TAF-1, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TAF-2, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TAU-1, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TAU-2, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TEF-1 (transcription enhancer element factor 1), transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VP16, transregulatory domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transcriptional regulation
(activation, domain, in fusion protein; ligand-dependent regulation of

transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Polyelectrolytes
(anionic; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Drug delivery systems
(injections, introduction of the inducible expression system by; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Electroporation
(introduction of the inducible expression system by; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Genetic element
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(intron, synthetic; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Gene therapy
Plasmid vectors
Protein sequences
cDNA sequences
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Progesterone receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Blood-coagulation factors
Interferons
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Transgene
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Polymers, uses
RL: MOA (Modifier or additive use); USES (Uses)
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Protein motifs
(mol. switch protein contg.; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Fusion proteins (chimeric proteins)
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mol. switch protein; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Steroid receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified);

PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mutated ligand-binding domain of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Genetic element
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(polyadenylation signal; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Muscle
(promoter specific for; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Mouse
(studies on; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Actins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.-, gene promoter; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT Interferons
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.alpha.; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 406440-61-7P 406440-62-8P 406440-63-9P
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 24991-23-9 25513-46-6, Poly-L-glutamic acid
RL: MOA (Modifier or additive use); USES (Uses)
(anionic polymer; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 84371-65-3, Mifepristone 96346-61-1, Onapristone 97747-88-1, ZK98734 105114-63-4, ZK112993 116948-83-5, Org31376 123916-70-1, Org31806 **155768-15-3, Org 33245** 155768-17-5, Org 33628 272129-59-6, 5-.alpha.-Pregnane-3,2-dione
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(inducer; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 9001-28-9P, Blood-coagulation factor IX 11096-26-7P, Erythropoietin
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 9002-89-5, PVA 9003-39-8, PVP 106392-12-5, Poloxamer
RL: MOA (Modifier or additive use); USES (Uses)
(nonionic polymer; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 406440-64-0 406440-65-1, DNA (synthetic intron cDNA) 406440-66-2, DNA (synthetic intron cDNA) 406440-67-3, DNA (synthetic intron cDNA) 406440-68-4 406440-69-5 406440-70-8 406440-71-9 406440-72-0 406440-73-1, DNA (plasmid pGS1694 cDNA) 406440-74-2, DNA (plasmid

pEP1666 cDNA)
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 12629-01-5, Human growth hormone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(poly (A) signal of; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 406448-19-9 406448-20-2 406448-22-4 406448-23-5 406448-25-7 406448-26-8 406448-27-9
RL: PRP (Properties)
(unclaimed nucleotide sequence; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

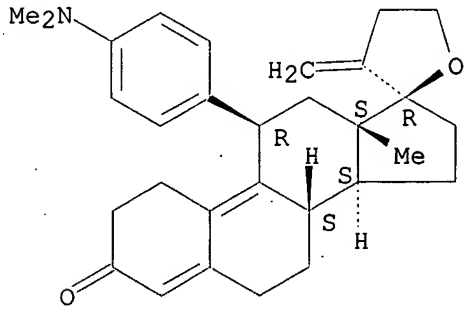
IT 406448-21-3 406448-24-6
RL: PRP (Properties)
(unclaimed protein sequence; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT 88160-20-7 105150-09-2
RL: PRP (Properties)
(unclaimed sequence; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

IT **155768-15-3, Org 33245**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(inducer; ligand-dependent regulation of transgene expression by a plasmid-based autoinducible GeneSwitch system for gene therapy application)

RN 155768-15-3 HCAPLUS
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L34 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:790317 HCAPLUS
DN 133:345161
TI Use of antiprogestagen **Org 33245** in combined therapy with progestagen-only preparations
IN **Coelingh Bennink, Herman Jan Tijmen; Deckers, Godefridus Hermanus Johanna; Dols, Paul Peter Marie Antonius; Orlemans, Everardus Otto Maria; Schoonen, Wilhelmus Gerardus Eduardus Joseph**
PA **Akzo Nobel N.V., Neth.**

SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-58
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	WO 2000066129	A2	20001109		WO 2000-EP3747	20000425	<--
	WO 2000066129	A3	20010419				
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM						
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
	BR 2000010070	A	20020115		BR 2000-10070	20000425	<--
	EP 1178807	A2	20020213		EP 2000-920742	20000425	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO						
	JP 2002543136	T2	20021217		JP 2000-615013	20000425	<--
	NO 2001005207	A	20011025		NO 2001-5207	20011025	<--
PRAI	EP 1999-201390	A	19990429	<--			
	WO 2000-EP3747	W	20000425	<--			

AB The antiprogestagen compd. **Org 33245** ((11.beta.,17.alpha.)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one) of formula (I) is suitability for being administered intermittently and can be used in combined therapy with progestagen-only prepns. for hormone replacement therapy or contraception. A contraceptive kit providing for the daily administration of a progestagen and the intermittent administration of antiprogestagen is also claimed.

ST antiprogestagen prostagen prepn contraceptive hormone replacement

IT Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiprogestins; use of antiprogestagen **Org 33245** in combined therapy with progestagen-only prepns.)

IT Menstrual disorder
(breakthrough bleeding treatment; use of antiprogestagen **Org 33245** in combined therapy with progestagen-only prepns.)

IT Contraceptives
Hormone replacement therapy
(use of antiprogestagen **Org 33245** in combined therapy with progestagen-only prepns.)

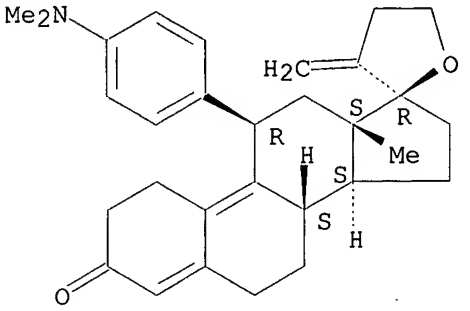
IT Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of antiprogestagen **Org 33245** in combined therapy with progestagen-only prepns.)

IT **155768-15-3, Org 33245**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of antiprogestagen **Org 33245** in combined therapy with progestagen-only prepns.)

IT **155768-15-3, Org 33245**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(use of antiprogestagen **Org 33245** in combined therapy with progestagen-only prepns.)
RN 155768-15-3 HCAPLUS
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L34 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:509883 HCAPLUS
DN 133:344644
TI Antiprogestins: Their mechanism of action and the consequences for compound selection by in vitro and in vivo studies
AU **Schoonen, W. G. E. J.**; Vermeulen, G. J.; **Deckers, G. H.**; Verbost, P. M.; Kloosterboer, H. J.
CS Lead Discovery Unit, N. V. Organon., Oss, 5340 BH, Neth.
SO Current Topics in Steroid Research (1999), 2, 15-54
CODEN: CTSRFV
PB Research Trends
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 1
AB A review with 185 refs. Antiprogestins can be used for a variety of clin. indications. These include clin. use for pregnancy interruption, labor management and anti-conception. Besides these applications, antiprogestins can be used for the treatment of endometriosis, uterine leiomyomata, breast tumors and meningiomas. The antiprogestins act via the progesterone receptor (PR) isoforms, for which distribution and expression are differently regulated among the various reprodn. assocd. tissues. The pivotal role of PR for female reprodn. has become clear with PR (A and B) and specific PR-A knock-out mice, which are infertile. The mechanism of action of antiprogestins through PR-A and -B depends on the PR-A/B ratio, the cellular and promoter context, the presence of protein kinase A activity, and the presence of co-activators and co-repressors. Finally the mol. structure of the antiprogestins themselves has a strong impact. RU 38486 (RU 486, mifepristone), a 19-norsteroid with an 11.beta.-(4-dimethylamino) (amino) Ph and a 17.alpha.-propynyl side chain, was the first potent antiprogestin identified. Its antagonistic bioactivity was shown in pregnancy interruption and anti-McPhail tests. Unfortunately, RU 486 has also an antiglucocorticoid activity. Improvement of this antiprogestagenic/antiglucocorticoid selectivity is required to reduce its adverse side effects. To achieve this goal new antiprogestins are still in development. In this review the pharmacol. profile of several newly developed antiprogestins is compared with five stds., i.e., RU 486, ZK 98299, ZK 112993, Org 31710 and Org 31806, using different tests. On the mol. level, in vitro studies can discriminate between ligand-receptor, reporter assays, receptor-DNA, and cellular

responses. Thereto receptor binding, receptor mediated transactivation, gel retardation and inhibition of breast tumor cell growth studies were carried out, resp. With respect to in vivo studies, three animal models exist for endometrium, i.e., pregnancy interruption, endometrium proliferation and menses induction, while breast tumor prevention can be seen as a beneficial effect for antiprogestins. Adverse effects for antiglucocorticoid in vivo activity are measured on thymus, adrenal and body wt. redn. and with in vitro binding and transactivation studies. All antiprogestins were tested in binding, transactivation, pregnancy interruption and endometrium proliferation tests. The most potent compds. were selected for in vitro and in vivo antiglucocortioid activity measurements. This complex set of assays is carried out to get a clear profile of the compds. and to make a proper selection taking data from all these assays into account. The four selected antiprogestins combine a 17--spiromethylene ether group with an 11.beta.-(4-dimethylamino)phenyl (**Org 33245**), 11.beta.-(4-acetyl)phenyl (Org 33628), (4-methylthio)phenyl (Org 33832) or (4-methoxy)phenyl (Org 33901) group and appeared to be among the most potent representatives of 38 different antiprogestins tested, stds. included. Since **Org 33245** , Org 33628 and/or Org 33832 were. More active in pregnancy interruption and menses induction tests than Org 33901, these compds. are considered for further evaluation. Org 33628 has been selected for further clin. development.

ST review antiprogestin progesterone receptor

IT Progesterone receptors

RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(antiprogestins in relation to mechanism of action and consequences for compd. selection by in vitro and in vivo studies)

IT Progestogens

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(antiprogestins; antiprogestins in relation to mechanism of action and consequences for compd. selection by in vitro and in vivo studies)

RE.CNT 184 THERE ARE 184 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L34 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:350601 HCAPLUS
DN 131:9627
TI Progestogen-antiprogestogen regimens as contraceptives
IN **Coelingh Bennink, Herman Jan Tijmen**
PA **Akzo Nobel N.V., USA**
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-57
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9925360	A2	19990527	WO 1998-EP7221	19981110
WO 9925360	A3	19990729		
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2309745	AA	19990527	CA 1998-2309745	19981110
AU 9921527	A1	19990607	AU 1999-21527	19981110

AU 747710 B2 20020523
EP 1030669 A2 20000830 EP 1998-965666 19981110
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
BR 9814136 A 20001003 BR 1998-14136 19981110
JP 2001523639 T2 20011127 JP 2000-520793 19981110
NZ 504351 A 20021025 NZ 1998-504351 19981110
NO 2000002475 A 20000712 NO 2000-2475 20000512
MX 200004610 A 20001110 MX 2000-4610 20000512
PRAI EP 1997-203543 A 19971114
EP 1998-201464 A 19980508
WO 1998-EP7221 W 19981110

AB An estrogen-free contraceptive is provided which does not have the bleeding-related drawbacks of conventional progestogen-only pills. Thus the invention is a contraceptive kit comprising a combined means for the simultaneous daily administration of a progestogen as the sole contraceptively effective ingredient and an anti-progestogen. Said combined means preferably is in the form of tablets having a normal contraceptive dose of the progestogen and low dose of the anti-progestogen.

ST progestogen antiprogestogen contraceptive; tablet progestogen antiprogestogen contraceptive

IT Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiprogestins; progestogen-antiprogestogen regimens as contraceptives)

IT Contraceptives
(oral; progestogen-antiprogestogen regimens as contraceptives)

IT Contraceptives
(progestogen-antiprogestogen regimens as contraceptives)

IT Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(progestogen-antiprogestogen regimens as contraceptives)

IT Drug delivery systems
(tablets; progestogen-antiprogestogen regimens as contraceptives)

IT 54024-22-5, Desogestrel 60282-87-3, Gestodene 84371-65-3, RU 486 110072-15-6, Org 30659 118968-41-5, Org 31710 155768-17-5, Org 33628 **225511-56-8 225511-57-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(progestogen-antiprogestogen regimens as contraceptives)

IT **225511-56-8 225511-57-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(progestogen-antiprogestogen regimens as contraceptives)

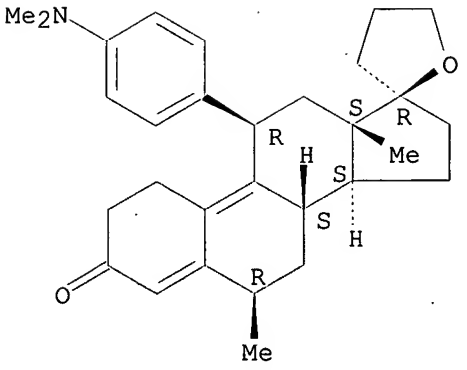
RN 225511-56-8 HCAPLUS

CN Spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methyl-, (6.beta.,11.beta.,17.beta.)-, mixt. with (17.alpha.)-13-ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol (9CI) (CA INDEX NAME)

CM 1

CRN 118968-41-5
CMF C30 H39 N O2

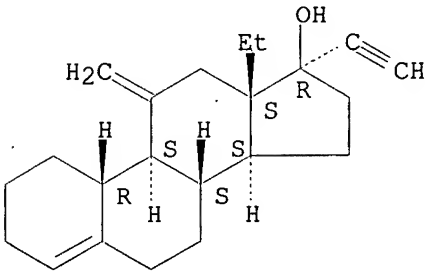
Absolute stereochemistry.



CM 2

CRN 54024-22-5
CMF C22 H30 O

Absolute stereochemistry. Rotation (+).

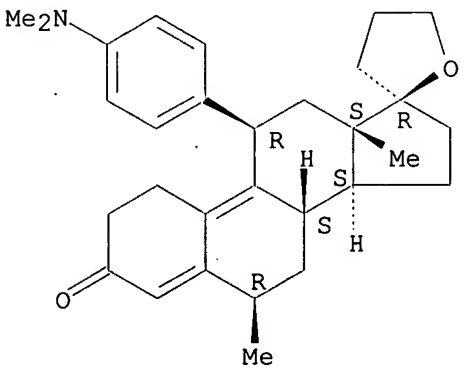


RN 225511-57-9 HCAPLUS
CN Spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methyl-, (6.beta.,11.beta.,17.beta.)-, mixt. with (17.alpha.)-17-hydroxy-11-methylene-19-norpregna-4,15-dien-20-yn-3-one (9CI) (CA INDEX NAME)

CM 1

CRN 118968-41-5
CMF C30 H39 N O2

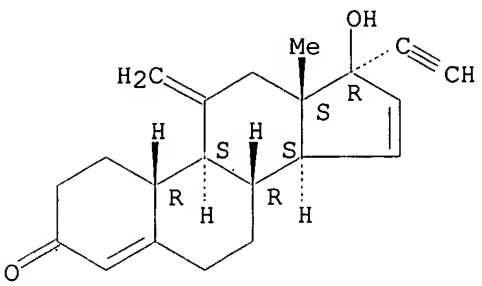
Absolute stereochemistry.



CM 2

CRN 110072-15-6
CMF C21 H24 O2

Absolute stereochemistry.



L34 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:320178 HCAPLUS
DN 129:63154
TI Human progesterone receptor A and B isoforms in CHO cells. II. Comparison of binding, transactivation and ED50 values of several synthetic (anti)progestagens in vitro in CHO and MCF-7 cells and in vivo in rabbits and rats
AU **Schoonen, W. G. E. J.**; Dijkema, R.; De Ries, R. J. H.; Wagenaars, J. L.; Joosten, J. W. H.; De Gooyer, M. E.; **Deckers, G. H.**; Kloosterboer, H. J.
CS Scientific Development Group, Department of Endocrinology, N. V. Organon, Oss, 5340 BH, Neth.
SO Journal of Steroid Biochemistry and Molecular Biology (1998), 64(3-4), 157-170
CODEN: JSBBEZ; ISSN: 0960-0760
PB Elsevier Science Ltd.
DT Journal
LA English
CC 2-4 (Mammalian Hormones)
AB The human progesterone receptor A and B isoforms (hPR-A and hPR-B) were stably transfected in Chinese Hamster Ovary (CHO) cells in the presence or absence of the mouse mammary tumor virus (MMTV) promoter and luciferase (LUC) reporter gene. In this way four stably transfected CHO cell lines, i.e. hPR-A, hPR-B, hPR-A-MMTV-LUC and hPR-B-MMTV-LUC cells, were prepd. HPR-A and -B isoforms were compared by binding and transactivation anal. for 14 progestagens and 7 antiprogestagens. Thereby Org 2058 was used as std. in both agonistic and binding assays and Org 31710 in antagonistic assays. The obtained data were compared with relative binding affinities (RBA) for both hPR-A and -B, which are present in human breast tumor MCF-7 cells, and with biopotency estns. with McPhail tests in rabbits and ovulation inhibition and pregnancy interruption tests in rats. The relative binding affinities of 14 progestagens and 7 antiprogestagens towards hPR-A, hPR-B or hPR-A/B of either CHO or MCF-7 cells were highly correlated with respect to ranking. This was also shown by the high correlation coeffs. between the RBA's of hPR-B and hPR-A in CHO cells (r = 0.983) and between those of hPR-B of CHO and hPR A/B of MCF-7 cells (r = 0.957). The transactivation data of the 14 progestagens and 7 antiprogestagens for the hPR-B-MMTV-LUC cells were compared with those for hPR-A-MMTV-LUC cells and showed no differences between both cell lines with exception of the progestagens Org 32704 and 33766 and the antiprogestagen **Org 33245**. Therefore only the

relative agonistic activities (RAA) and relative antagonistic activities (RANTA) of hPR-B-MMTV-LUC cells were compared with RBA values of hPR-B, showing a high similarity in ranking for the tested compds., and high correlation coeffs. of r = 0.91 and r = 0.97, resp. Remarkably, RBA's were 1.6 fold higher than RAA's and RANTA's. These in vitro RBA, RAA and RANTA values for hPR-B were checked for their pharmacol. relevance by in vivo biopotency measurements with the 14 progestagens and 7 antiprogestagens in rabbits and rats. The in vitro binding and transactivation potencies of progestagens appeared to be very predictive for in vivo anal. on endometrium proliferation in rabbits in the McPhail test with correlation coeffs. of r = 0.81 and r = 0.87, while ovulation inhibition in rats correlated less well with r = 0.516 and r = 0.65. On the other hand, the antiprogestagenic potencies found with binding and transactivation assays had a good correlation with the potencies in the pregnancy interruption test in rats for all antiprogestagens tested, being r = 0.849 and r = 0.744, resp. In conclusion, the binding and transactivation potencies for the tested compds. in hPR-A and -B cell lines showed in general a good resemblance. The transactivation studies with hPR-B-MMTV-LUC cells indicated that ranking of compds. was fairly identical to binding anal. and could be used for pre-screening of the (anti)-progestagenic bioactivity in the McPhail test in rabbits, the ovulation inhibition test and the pregnancy interruption test in rats. Therefore, this transactivation assay can replace binding assays. Moreover, direct pre-screening of agonists, antagonists and partial antagonists is even possible in this in vitro bioassay, making transactivation assays for a particular class of chem. compds. a valuable pre-screening tool for in vivo studies.

ST progesterone receptor isoform transfected CHO cell; progestagen antiprogestagen prescreening transfected CHO cell

IT Animal cell line
(CHO; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(MMTV; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)

IT Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiprogestins; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)

IT Reporter gene
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(luciferase; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)

IT Mouse mammary tumor virus
(promoter; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)

IT Transcriptional regulation
(transactivation assay; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)

IT Drug screening
Transformation, genetic
(use of transfected CHO cells expressing human progesterone receptor A

and B isoforms to prescreen progestagens and antiprogestagens)
IT Progestogens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)
IT Progesterone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)
IT 9014-00-0, Luciferase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(reporter gene; use of transfected CHO cells expressing human progesterone receptor A and B isoforms to prescreen progestagens and antiprogestagens)
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L34 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:631157 HCAPLUS
DN 121:231157
TI Preparation of 17-spiromethylene steroids
IN Hamersma, Johannes Antonius Maria; **Orlemans, Everardus Otto Maria**; Rewinkel, Johannes Bernardus Maria
PA **AKZO N. V., Neth.**
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07J021-00
ICS C07J031-00; C07J041-00; C07J043-00; C07J053-00; A61K031-58
ICA C07J071-00; C07J051-00
CC 32-6 (Steroids)

Section cross-reference(s): 2

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 582338	A2	19940209	EP 1993-202204	19930726
	EP 582338	B1	19991020		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CA 2100514	AA	19940130	CA 1993-2100514	19930714
	ZA 9305131	A	19940209	ZA 1993-5131	19930715
	AU 9342037	A1	19940203	AU 1993-42037	19930716
	AU 665430	B2	19960104		
	AT 185812	E	19991115	AT 1993-202204	19930726
	ES 2140436	T3	20000301	ES 1993-202204	19930726
	NO 9302723	A	19940131	NO 1993-2723	19930728
	CN 1084857	A	19940406	CN 1993-108470	19930728
	CN 1054133	B	20000705		
	US 5712264	A	19980127	US 1993-98665	19930728
	JP 06157587	A2	19940603	JP 1993-188460	19930729
	JP 3418428	B2	20030623		
	US 5854235	A	19981229	US 1997-962798	19971103
	HK 1002011	A1	20000519	HK 1998-101025	19980211
PRAI	EP 1992-202339	A	19920729		
	EP 1993-201657	A	19930610		
	US 1993-98665	A3	19930728		

OS MARPAT 121:231157

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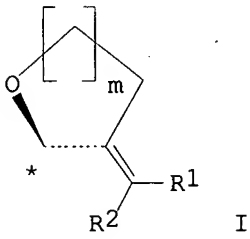

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AB The invention relates to a steroid deriv. [I; R1, R2 = H, Me, halo; m = 1, 2] which steroidal skeleton is bound at carbon atom 17 to a spiromethylene ring of the formula: wherein R1 and R2 are independently selected from the group consisting of hydrogen, Me, and halogen; m is 1 or 2; and the asterisk denotes carbon atom 2 of the spiromethylene ring which is carbon atom 17 (or carbon atom 17.alpha. of a homosteroid skeleton) of the steroid. The steroids have progestational or antiprogestational activity (no data). About 80 title compds. were prepd.

ST spiromethylene steroid prepn progestational antiprogestational

IT Progestogens
RL: RCT (Reactant); RACT (Reactant or reagent)
(spiromethylene steroids)

IT Steroids, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(spiro-, prepn. of, for their progestational or antiprogestational activity)

IT 158293-88-0P 158293-89-1P 158293-90-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for spiromethylene ring)

IT 5571-36-8P 139297-98-6P 155768-26-6P 155768-27-7P 155768-28-8P
155768-29-9P 155768-32-4P 155768-33-5P 155773-65-2P 155806-63-6P
158294-15-6P 158294-38-3P 158294-39-4P 158294-40-7P 158294-41-8P
158294-42-9P 158294-43-0P 158294-44-1P 158294-45-2P 158294-46-3P
158294-48-5P 158294-49-6P 158294-50-9P 158294-51-0P 158294-52-1P

158294-53-2P 158294-54-3P 158294-55-4P 158294-56-5P 158294-57-6P
158294-58-7P 158294-59-8P 158294-60-1P 158294-61-2P 158294-62-3P
158294-63-4P 158294-64-5P 158294-65-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for spiromethylene steroids)

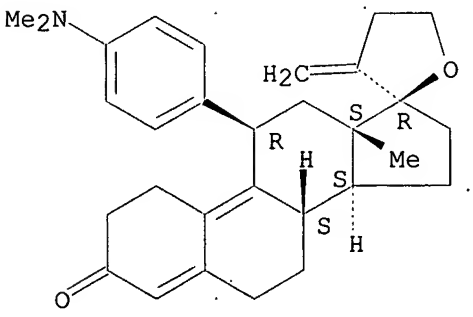
IT **155768-15-3P** 155768-16-4P 155768-17-5P 155768-18-6P
155768-19-7P 155768-20-0P 155768-21-1P 155768-22-2P 155768-23-3P
155768-24-4P 158293-75-5P 158293-76-6P 158293-77-7P 158293-78-8P
158293-79-9P 158293-80-2P 158293-81-3P 158293-82-4P 158293-83-5P
158293-84-6P 158293-85-7P 158293-86-8P 158293-87-9P 158293-91-5P
158293-92-6P 158293-93-7P 158293-94-8P 158293-95-9P 158293-96-0P
158293-97-1P 158293-98-2P 158293-99-3P 158294-00-9P 158294-01-0P
158294-02-1P 158294-03-2P 158294-04-3P 158294-05-4P 158294-06-5P
158294-07-6P **158294-08-7P 158294-09-8P** 158294-10-1P
158294-11-2P 158294-12-3P 158294-13-4P 158294-14-5P 158294-15-6P
158294-16-7P 158294-17-8P 158294-18-9P 158294-19-0P 158294-20-3P
158294-21-4P 158294-22-5P 158294-23-6P 158294-24-7P 158294-25-8P
158294-26-9P 158294-27-0P 158294-28-1P 158294-29-2P 158294-30-5P
158294-31-6P 158294-32-7P 158294-33-8P 158294-34-9P 158294-35-0P
158294-36-1P 158294-37-2P 158294-47-4P 158294-84-9P 158411-74-6P
158411-75-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for its progestational or antiprogestational activity)

IT 107-21-1, 1,2-Ethanediol, reactions 122-51-0, Triethyl orthoformate
1779-49-3, Methyltriphenylphosphonium bromide 2863-88-9 13169-00-1,
1-Methoxy-1,2-propadiene 68978-74-5 68978-75-6 158293-88-0
158294-66-7 158294-67-8 158294-68-9 158294-69-0 158294-70-3
158294-71-4 158294-72-5 158294-73-6 158294-74-7 158294-75-8
158294-76-9 158294-77-0 158294-78-1 158294-79-2 158294-80-5
158294-81-6 158294-82-7 158294-83-8, 2-Bromo-5-trimethylsilyloxy-1-pentene
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of spiromethylene steroids)

IT **155768-15-3P 158294-08-7P 158294-09-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for its progestational or antiprogestational activity)

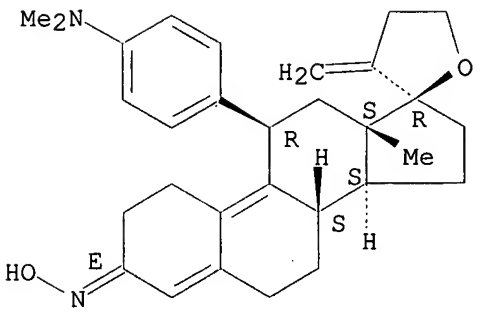
RN 155768-15-3 HCAPLUS
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



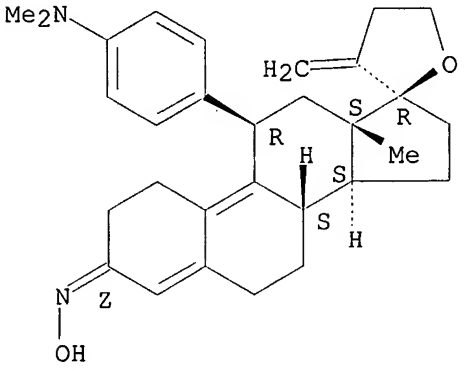
RN 158294-08-7 HCAPLUS
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3E,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 158294-09-8 HCAPLUS
CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, oxime, (3Z,11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L34 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:435986 HCAPLUS
DN 121:35986
TI Preparation of 17-spirofuran-3'-ylidene steroids as antiprogestins
IN Hemersma, Johannes Antonius Maria; **Orlemans, Everardus Otto Maria**
PA **AKZO N. V., Neth.**
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07J021-00
ICS C07J041-00; C07J031-00; A61K031-58
ICA C07J071-00
CC 32-6 (Steroids)
Section cross-reference(s): 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 549041	A1	19930630	EP 1992-203923	19921215
	EP 549041	B1	19951011		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	ZA 9209315	A	19930524	ZA 1992-9315	19921201
	CA 2084431	AA	19930621	CA 1992-2084431	19921203
	AU 9230093	A1	19930624	AU 1992-30093	19921211
	AU 655858	B2	19950112		
	NO 9204857	A	19930621	NO 1992-4857	19921215

	AT 128983	E	19951015	AT 1992-203923	19921215
	ES 2081040	T3	19960216	ES 1992-203923	19921215
	JP 05255380	A2	19931005	JP 1992-338830	19921218
	US 5292878	A	19940308	US 1992-994039	19921221
PRAI	EP 1991-203366		19911220		

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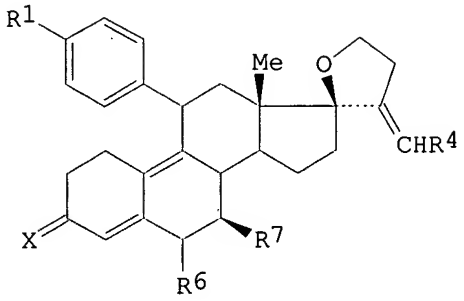

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AB Title compds. (I; R1 = NR2R3, acyl, OH, alkoxy, etc.; R2-R4 = H, alkyl; R6,R7 = H; 1 of R6,R7 = H and the other = alkyl; X = O,H2, H and OH, etc.) were prepd. as antiprogestins (no data). Thus, (17.beta.)-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-one was converted in 10 steps to (11.beta.,17.alpha.)-17,23-epoxy-11-(4-dimethylaminophenyl)-19,24-dinorchola-4,9,20-trien-3-one.

ST spirofuranylidene steroids prepn antiprogestin

IT Progestogens
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibitors, spirofuranylidene steroids)

IT 155768-26-6P 155768-27-7P 155768-28-8P 155768-29-9P 155768-30-2P
155768-31-3P 155768-32-4P 155768-33-5P 155773-65-2P 155806-63-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of antiprogestin)

IT **155768-15-3P** 155768-16-4P 155768-17-5P 155768-18-6P
155768-19-7P 155768-20-0P 155768-21-1P 155768-22-2P 155768-23-3P
155768-24-4P 155768-25-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiprogestin)

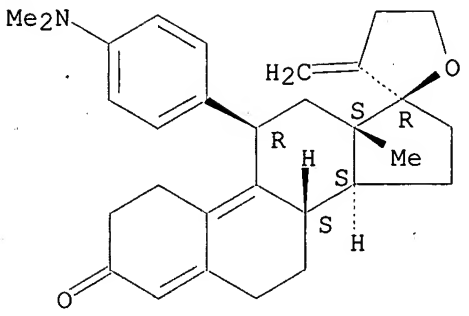
IT 5571-36-8 7353-91-5, 4-Dimethylaminophenylmagnesium bromide
13169-00-1, 1-Methoxy-1,2-propadiene 68978-75-6 155768-34-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of antiprogestin)

IT **155768-15-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiprogestin)

RN 155768-15-3 HCAPLUS

CN 19,24-Dinorchola-4,9,20-trien-3-one, 11-[4-(dimethylamino)phenyl]-17,23-epoxy-, (11.beta.,17.alpha.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


Me2N
H2C
O
S
R
R
H
Me
S
S
H
O